CERTIFIED MAIL
RETURN RECEIPT REQUESTED

December 3, 2001

Mr. Gary Buehler
Director, Office of Generic Drugs
Food and Drug Administration
7500 Standish Place, HFD-600
Rockville, MD 20855

Dear Mr. Buehler:

This letter is written to present new data reflecting a serious concern; that of the Mylan generic estradiol transdermal system being inequivalent to the reference listed drug (RLD), Climara® once-a-week estradiol transdermal system, when used at the same application sites and according to the labeling directions.[1] The Mylan estradiol transdermal system and Climara® are now unequivocally shown to be bioinequivalent at the buttock application site; therefore, the Mylan labeling cannot support the buttock as an application site. In addition, the adhesion of the Mylan estradiol transdermal system is significantly worse than that observed of the RLD. Therefore, we request that the Office of Generic Drugs change the Therapeutic Equivalence Code from A-rated to B-rated and not recommend the Mylan estradiol transdermal system as a generic substitute to Climara®.

Mylan was allowed to establish its product's bioequivalence to Climara® solely on the basis of the patch's use on the abdomen, and granted labeling comparable to the RLD allowing for the product to be affixed either to the users' lower abdomen or to the upper quadrant of the buttock. We presume that this labeling was granted under the assumption that bioequivalence at one application site is a surrogate for other application sites. Berlex in conjunction with 3M have conducted a clinical bioequivalence crossover study, however, and determined that this assumption is incorrect. When applied to the buttock, the Mylan estradiol transdermal system is not bioequivalent to the RLD, but instead delivers statistically significantly more estradiol into the bloodstream.[2] Because of its bioinequivalence, the labeling for the Mylan estradiol transdermal system should not allow placement of the patch on the buttock. Further, if the label is changed

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[1] We have expressed our concern previously in a Citizen's Petition (June 12, 1998, Docket #98-0434/CP1), in which we provided evidence that there were substantial site differences in absorption of estradiol between the abdomen and buttock that may be formulation dependent, and urged bioequivalence testing at both sites for the Mylan generic.

[2] A commentary on the Clinical Study No. 304100 is attached as Appendix 1, and a copy of the final study report is found in Appendix 2. Results of this study showed that the rate of estradiol absorption for the Mylan product exceeds the acceptable statistical parameters of bioequivalence. The 90% confidence interval for the maximum serum level of estradiol (C_{max}) ranged from 107% to 126% of the C_{max} for Climara® (p=0.004), exceeding the 125% acceptable upper limit, and was statistically significantly different. In addition, application site reactions, skin irritation, and patch lifting were more frequent with the Mylan product. Therefore, the two products are not bioequivalent. This study has been submitted for publication in the Journal of Clinical Pharmacology.

to appropriately omit application to the buttock site, the current labeling for Mylan's estradiol transdermal system renders the drug misbranded under Sections 502 (a), (f), and (j) of the FDC Act.

In addition, results from the crossover study demonstrate that there is a pharmacoeconomic impact of the above findings. Since there is decreased adhesion and increased costs associated with replacing or taping the Mylan estradiol transdermal system as compared to the RLD, there does not appear to be a cost savings associated with using the generic product.[3]

The clinical significance of this bioinequivalence lies in the concern regarding serum estradiol posed to the user. Women who apply the Mylan estradiol transdermal system to the buttock can expect to realize rates of estradiol absorption into the blood stream that are higher than those FDA deemed to be safe in approving the Climara® RLD.

We urge you to consider these data to be extremely important, and to realize the risk to the users of the Mylan estradiol transdermal system. Our expectation is that you find that these statistically significant differences between the Mylan estradiol transdermal system and Climara® make the products bioinequivalent, and that the Mylan product should not be listed as an A-rated generic.

We would like to discuss these issues with you at your earliest convenience. We plan to call you during the week of December 10th to set up a conference time. Please do not hesitate to contact the undersigned if you have any questions or if you would like us to provide you with any additional information.

Very truly yours,

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[3] Jones, J.P., Rowe, M.M., and Harrison, L.I. 2001. Replacing branded estradiol transdermal systems with generic alternatives does not result in a cost savings. Abstract to be presented at the Academy of Managed Care Pharmacy, 14th Annual Meeting, Salt Lake City, UT, April 3-6, 2002.